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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/745,605	Applicant(s) STARLING ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5-29-01 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-5,15-26 and 42 is/are pending in the application.

4a) Of the above claim(s) 6-14,27-41 and 43-52 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-5,15-26,and 42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☒ Interview Summary (PTO-413) Paper No(s). 11 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-52 are pending.

2. Applicant's election without traverse of Group I claims 1-5, 15-26, 42-43 and 50, and radioisotope as the species in Paper No. 10 is acknowledged.

However, claim 50 was inadvertently included in Group I. In a telephonic interview Examiner indicated that in the restriction requirement, claim 50 was inadvertently included in Groups I-III and claim 50 needed to be withdrawn from these Groups because claim 50 does not read on the isolated nucleic acids of Groups I-III as indicated in the restriction mailed 2-8-02. Applicant agreed with the above clarification.

In addition, a clear and obvious typographical error occurred in the restriction wherein claim 43 which reads on protein was included in Groups I-III which are drawn to isolated nucleic sequences. Claim 43 should belong to Groups IV-VI. Therefore claim 43 is withdrawn to a nonelected invention.

3. Claims 6-14, 27-41, and 43-52 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-5, 15-26, and 42 are under examination as they read on an isolated nucleotide sequence of SEQ ID NO:1, encoding a polypeptide of SEQ ID NO 4, vectors, host cells and methods of producing the polypeptide. Furhtermore, the claims read on the elected species, radioisotope.

5. Claims 15-26 and 42 are objected to because they are dependent on non-elected claims 6 and 11.

6. Applicant's IDS, filed 3-26-01, is acknowledged.

However, the PTO-1449 form and the references can not been found. Applicant is required to resubmit the form PTO-1449 and the references.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 16 and 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The recitation of "hybridizes under stringent conditions" in claim 16 is ambiguous. Although the specification discloses on pages 31-32 general parameters for calculating such conditions, in the absence of a clear definition of the metes and bounds of this phrase it is unclear which conditions are actually claimed.

B) Claims 21 and 22 have no antecedent basis in base claim1, because claim 1 recites nucleic acid molecule per se, whereas a labeled nucleic acid is recited in claims 21 and 22. It is suggested that claim 21 be changed to "A labeled nucleic acid molecule, wherein the nucleic acid molecule of claim 1 is labeled with detectable marker" and claim 22 be changed to "The labeled nucleic acid molecule of claim 21, wherein the detectable marker is ...".

9. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

10. Claims *1-5, 15-26, and 42* are rejected tounder 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility.

Applicants are directed to the Revised Interim Utility Guidelines, Federal Register, Vol. 64, No.244, pages 71427-71440, Tuesday December 21, 1999. In keeping with the revised utility guidelines and corresponding training materials (available on the PTO Website), none of the disclosed uses is a specific and/or substantial use.

The instant application has provided a description of an isolated nucleic acid encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of the protein or its significance. The instant specification asserts that the protein may be a potential target for disease such as inflammation, cancer, and immune disorders (page 54, lines 5-6). The specification asserts that arteriosclerosis, asthma, autoimmune anemia, acquired immunodeficiency syndrome (AIDS), bursitis, cholecystitis, cirrhosis, crohn's disease, atopic dermatitis, diabetes, mellitus, emphysema, atrophic gastritis, inflammatory bowel disease, multiple sclerosis, myasthenia gravis, myocardial or pericardia inflammation, osteoarthritis, osteoporosis, psoriasis, Reiter's syndrome, rheumatoid arthritis, and systemic lupus erythematosus (page 54, lines 21-28) could be treated or prevented by administration of a therapeutically effective amount of APEX or an agonist thereof. The specification also asserts that administration of a therapeutically effective amount of APEX or an agonist thereof could

treat or prevent cancer such as adrenal gland, bladder, bone, bone marrow, breast, cervix, gall bladder, gastrointestinal tract, kidney, liver, lung, muscle, ovary, pancreas, prostrate, salivary glands, skin, spleen, testis, thymus, thyroid and uterus (page 54, lines 29-31 and page 55 line1).

These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the CD2 subfamily- similar protein (APEX). The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner V. Manson*, 148 U.S. P. Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S. C. § 101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility.

The instant claims are drawn to a nucleic acid encoding a polypeptide of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion CD2 subfamily-like protein (APEX) of the instant application was, as of the filling date, useful for regulating adhesion and generating co-stimulatory signals to mediate leukocyte proliferation, differentiation, migration, or activation (page 16, lines 11-18). Until some actual and specific significance can be attributed to the protein identified in the specification as APEX, or the gene enoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

The nucleic acid of the instant invention and the protein encoded thereby are compounds which share some structural similarity with CD2 subfamily based on sequence similarity. The CD2 subfamily includes CD2, CD58, CD48, CD59, CD84, Ly9, 2B4, and CDw150 (SLAM). These proteins share several common structural domains such as extracellular Ig-like domains, a transmembrane domain or a glycosylphosphatidylinositol (GPI)-anchor moiety. CD84 and Ly9 functions have not been elucidated to date while SLAM has been shown to enhance antigen-specific proliferation and cytokine production by CD4+ T cells. It is not clear if the protein of the instant application would have the same function to enhance antigen-specific proliferation and cytokine production. Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the

multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). To employ a protein of the instant invention in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility which, alone, does not support patentablility. Since the instant specification does not disclose a credible "real world" use for APEX, then the claimed invention as disclosed does not meet the requirement of 35 U.S.C. § 101 as being useful.

11. Claims 1-5, 15-26 and 42 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Further, besides an isolated nucleic acid molecule of SEQ ID NO: 1 encoding amino acid SEQ ID NO: 4 the specification fails to provide any guidance as to how to make any isolated nucleic acid molecule encoding APEX-1 in claim 1; any isolated nucleic acid molecule wherein APEX-1 has an extracellular domain encoded by nucleotide sequences beginning with thymine (t) at position 108 and ending with cytosine (c) at position 716 in claim 5; any isolated variant having at least 70% polynucleotide sequence identity to the isolated nucleic acid molecule encoding APEX-1 in claim 15; any isolated polynucleotide which hybridizes under stringent conditions to the complement of polynucleotide encoding APEX-1 in claim 16; or any nucleic acid molecule comprising a nucleotide sequence which is complementary to the isolated nucleic acid molecule encoding APEX-1 in claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only a single nucleic acid sequence (SEQ ID NO:1) encoding a single polypeptide (SEQ ID NO:4). The instant claims encompass in their breadth *any* nucleic acid encoding a polypeptide (nucleic acid encoding APEX-1); or *any* nucleic acid that "hybridizes under stringent conditions"; or nucleic acids variants (with at least about 70% polynucleotide sequence identity).

There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make the various nucleic acids recited in the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences.

The term "has" in claim 5 is open ended and extend the nucleic acid to encode additional undisclosed amino acid sequences. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to the same structure of a nucleic acid encoding APEX-1. Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the lack of sufficient guidance and working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NO: 4 that after modification will retain the same structure of APEX-1 protein is unpredictable. The instant claim language encompass fragment. For example, claims 5 recites an isolated nucleic acid wherein APEX-1 has an extracellular domain. Such a recitation does not require that the nucleic acid encode the full length sequence set forth in SEQ ID NO:4; but rather encompasses *fragments* specially with open ended language as noted supra.

The fact that two nucleic acid sequences will hybridize under stringent conditions does not in and of itself require that the two sequences share any functional activity. Thus the same observations apply to the recitation of "a nucleic acid that hybridizes under stringent conditions" as were noted above with respect to "percent identity" language. Further, it was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible with respect to the citation in claim 15 "variant having 70% polynucleotide sequence identity" in the absence of a clear recitation that the identity is over the full length of SEQ ID NO:1 the claim reads on fragments. Meinkoth *et al* in Analytical Biochemistry (138:267-284, 1984) indicate factors that affect nucleic acid hybridization such as probes length of the shortest chain in the duplex, the ionic strength , base composition and the concentration of the helix destabilizing agents (page 269, left column 2nd and 3rd paragraphs in particular).

The claims as written encompass a broad genus of polynucleotides with a large number of possibilities with regard to the length of the nucleic acid sequence. Further, making changes up to 30% of an nucleic acid sequence does not provide maintaining the same three dimensional structure as the 100% identity *over the full length of SEQ ID NO:1.* The instant claim language appears to encompass polynucleotide variants. For example, claims 15 and 16 recite a nucleic acid a variant having at least 70% polynucleotide

sequence identity and a polynucleotide which hybridizes to SEQ ID NO:1. Such a recitation does not require that the nucleic acid encode the full length sequence set forth in SEQ ID NO:1; but rather encompasses any nucleic acid sequence comprising either the full length of SEQ ID NO:1 or *any variant*. The specification does not appear to have provided any working examples of any variants. Thus it would require undue experimentation of the skilled artisan to determine which variants of SEQ ID NO:1 would identify nucleic acid of SEQ ID NO:1.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the instantly recited nucleic acid sequences and still encode a polypeptide is unpredictable, as is the identity of which variant would encode APEX-1; thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

12. Claims 1, 5, 15-26 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of nucleic acid molecule of SEQ ID NO: 1 encoding amino acid of SEQ ID NO:4.

Applicant is not in possession of make any isolated nucleic acid molecule encoding APEX-1 in claim 1; any isolated nucleic acid molecule wherein APEX-1 has an extracellular domain encoded by nucleotide sequences beginning with thymine (t) at position 108 and ending with cytosine (c) at position 716 in claim 5; any isolated variant having at least 70% polynucleotide sequence identity to the isolated nucleic acid molecule encoding APEX-1 in claim 15; any isolated polynucleotide which hybridizes under stringent conditions to the complement of polynucleotide encoding APEX-1 in claim 16; or any nucleic acid molecule comprising a nucleotide sequence which is complementary to the isolated nucleic acid molecule encoding APEX-1 in claim 17.

Applicant has disclosed only nucleic acid of SEQ ID NO: 1; therefore, the skilled artisan cannot envision all the contemplated nucleic acid sequence possibilities recited in the instant claims. Consequently, conception in the above cases cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying

characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

A description of a genus of nucleic acid sequences may be achieved by means of a recitation of a representative number of the polynucleotide variants having 70% polynucleotide sequence identity; polynucleotide sequences which hybridizes under stringent conditions to complement of polynucleotide encoding APEX-1 or nucleic acid molecules wherein APEX-1 has an extracellular domain falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 3-5 and 15-19 are rejected under 35 U.S.C. 102(a) as being anticipated by WO996308 (Dec 9, 1999).

The WO996308 publication teaches a 1,076 isolated nucleic acid molecule encoding human myocardium protein-7 (MP-7), wherein MP-7 has the amino acid sequence shown in the instant claimed SEQ ID NO: 4 (see Figure 170 and sequence alignment in particular). The reference nucleic acid sequence begins with adenine (a) at position 42 and ends with guanine (g) at position 1049 of the claimed SEQ ID NO:1 (see sequence alignment in particular). The WO996308 publication further teaches a nucleotide sequence beginning with thymine (t) at position 108 and ending with cytosine (c) at position 716 of SEQ ID NO:1 (see Figure 170 and sequence alignment in particular). The reference nucleic acid molecule is a variant having 100% polynucleotide sequence identity to the polynucleotide encoding APEX-1. The reference polynucleotide is a sense sequence that would hybridize under stringent conditions to complement of polynucleotide encoding APEX-1. Claim 17 is included because complementary nucleic acids are intrinsic properties of the nucleic acid sequence because DNA strands are produced by copying preexisting DNA strand wherein the DNA from which the new strand is copied is called a template and the first copy has a complementary sequence. The terms "enoded" and "has" in instant claims 4 and 5 are open-ended. They would open up the claims to include the reference 1,076 nucleic acid moleucle.

The reference teachings anticipate the claimed invention.

15. Claims 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al (GenBand Accetion No. H73135 (1995)).

Hillier *et al* teach a 436 polynucleotide having 100% polynucleotide sequence identity to the polynucleotide at positions (49-306) of the claimed SEQ ID NO: 1. The reference polynucleotide is a sense sequence that would hybridize under stringent conditions to complement of polynucleotide encoding APEX-1. Claim 17 is included because complementary nucleic acids are intrinsic properties of the nucleic acid sequence because DNA strands are produced by copying preexisting DNA strand wherein the DNA from which the new strand is copied is called a template and the first copy has a complementary sequence. The term "having" in instant claim 15 is open-ended. It would open up the claim to include the reference 436 polynucleotide. In addition, the term "variant" in the instant claim 15 includes different forms of the gene including deletions and therefore, the claim reads on the reference nucleic acid sequence.
The reference teachings anticipate the claimed invention.

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO996308 in view of Adams el al (biochemistry of the nucleic acids)

The teachings of WO996308 publication have been discussed, supra.

The claimed invention differs from the combined reference teachings only by the recitation of the nucleic acid molecule is RNA (claim 18) wherein said RNA is mRNA (claim 20).

Adams *et al* teach that RNAs are synthesized from the complementary strand of duplex DNA which are catalysed by enzymes known as DNA-dependent RNA polymerases, the resulting mRNAs are used as coded messages for the synthesis of protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the DNA taught by the WO996308 publication to synthesis mRNA taught by the Adams et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the resulting mRNAs are used as coded messages for the synthesis of protein as taught by the Adams *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO996308 in view of U.S. Patent No. 6,134,002.

The teachings of WO996308 publication have been discussed, supra.

The claimed invention differs from the combined reference teachings only by the recitation of the nucleic acid molecule is labeled with detectable marker (claim 21) wherein said detectable marker is radioisotope (claim 22).

The '002 patent teaches that one way of detection and analysis of gel bands can be accomplished by using radioisotope labeled DNA. The radioactive gel slabs containing the separated DNA fragments are exposed overnight to film. After development of the x-ray film, the sequence or size of the DNA separated fragments are read directly from the images on the film.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to label the DNA taught by the WO996308 publication using the radioisotope taught by the '002 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because radioisotope labeled DNA allows the detection and analysis of the gel bands be accomplished as taught by the '002 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claims 23-26 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO996308 in view of Darnell *et al.*

The teachings of WO996308 publication have been discussed, supra.

The claimed invention differs from the combined reference teachings only by the recitation of a vector (claim 23), a host vector system in suitable host (claim 24) wherein said suitable host is a bacterial cell (claim 25) or an eukaryotic cell (claim 26) and a method for producing the APEX-1 protein (claim 42).

Darnell et al teach that in order to prepare an unlimited amount of a pure gene, a vector containing the gene can be grown in a host cell and DNA extracted. Darnell *et al* also teach an expression vector in order to take advantage of "bacterial tricks" that increase mRNA synthesis to produce large quantities of desired proteins using a eukaryotic vector and host cell, or a prokaryotic and bacterial vector and host cell (page 255-258 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the DNA taught by the WO996308 publication using the vectors, host cells and the method of producing the polypeptide as taught by Darnell *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because a vector containing the a gene that grown in a host cell offers to prepare an unlimited amount of a pure gene as well as to produce large quantities of desired proteins as taught by Darnell *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

21. **1. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

22. It is appears that nucleotide sequence of SEQ ID NO:1 is free of prior art.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
May 31, 2002

Christina Chan

CHRISTINA CHAN
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